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# Association Between Serum IL-8 Concentrations and Severity of Knee Osteoarthritis: An Exploratory Cross-Sectional Study

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## ABSTRACT

**Introduction:** Osteoarthritis (OA) is a chronic degenerative disorder of the joints that progresses over time, with inflammation playing a key role in its underlying mechanisms. Interleukin-8 (IL-8), a pro-inflammatory cytokine that participates in immune responses and neutrophil migration, has been associated with the process of cartilage breakdown in OA. This study was conducted to analyze the association between serum IL-8 concentrations and the radiographic severity of knee OA as exploratory evidence to enhance understanding of OA pathophysiology.
**Method:** This exploratory observational research applied a cross-sectional approach in patients diagnosed with knee OA. Seven participants were enrolled through total sampling at the Larasati Pondok Osteoarthritis Elderly Health Center, Faculty of Medicine, Wijaya Kusuma University, Surabaya. Radiographic severity of OA was determined using the Kellgren–Lawrence grading system. Venous blood specimens were obtained to determine serum IL-8 concentrations as an indicator of systemic inflammation.
**Results:** Statistical analysis demonstrated a significant inverse correlation between serum IL-8 concentrations and OA severity ($r = -0.866$, $P = 0.012$). These results indicate that IL-8 concentrations in serum are relatively elevated in the early phase of OA and tend to decline as the disease progresses.

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**Conclusion:** The findings of this exploratory study indicate that serum IL-8 may represent systemic inflammatory activity during the early stages of knee OA and holds potential as a biomarker candidate for future investigation. Further longitudinal studies involving larger sample sizes are necessary to validate its clinical relevance for OA detection and disease monitoring.

**Keywords:** Cartilage, inflammation, interleukin-8, joint diseases, osteoarthritis, risk factors

## Introduction

Osteoarthritis (OA) is a long-term degenerative joint condition marked by the gradual breakdown of articular cartilage, changes in the subchondral bone, development of osteophytes, and inflammation of the synovial membrane, all of which contribute to joint pain and reduced functional capacity.[1,2] OA represents a major contributor to musculoskeletal disability in the elderly population and places a considerable strain on healthcare systems worldwide. Data from the Global Burden of Disease study indicate that OA affects hundreds of millions of people globally, with its prevalence rising alongside population aging and the growing occurrence of risk factors such as obesity and joint trauma. The worldwide prevalence of knee OA is estimated at around 16% among adults and exceeds 20% in individuals older than 40 years.[3]

Epidemiological studies show that the worldwide burden of OA has risen markedly since 1990 and is expected to keep increasing through 2050, in line with demographic shifts and the expanding prevalence of metabolic risk factors, including diabetes mellitus. Beyond its impact on individual quality of life, OA also creates significant economic pressure on healthcare systems because of the growing need for both conservative treatments and surgical interventions such as joint arthroplasty.[4,5]

From a pathophysiological perspective, OA is no longer viewed solely as a degenerative condition but as a multifactorial disorder characterized by persistent low-grade inflammation. This inflammatory response arises through interactions between chondrocytes, synoviocytes, immune cells, and various inflammatory mediators, including cytokines and chemokines. Key proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) contribute significantly to extracellular matrix breakdown by promoting the activity of proteolytic enzymes, including matrix metalloproteinases (MMPs) and aggrecanases. In addition, these cytokines enhance chemokine production, facilitating immune cell infiltration into synovial tissue and thereby intensifying inflammation and

progressive joint damage.[1,6,7]

Interleukin-8 (IL-8) is a proinflammatory chemokine involved in the inflammatory mechanisms underlying OA. It is secreted by multiple cell types, including chondrocytes, synoviocytes, and immune cells, and functions as a chemoattractant for neutrophils. Activation of neutrophils within the joint environment may promote cartilage breakdown through the release of proteolytic enzymes and inflammatory mediators. Furthermore, IL-8 has been shown to stimulate chondrocyte differentiation and hypertrophic changes, as well as increase the expression of matrix metalloproteinase-13 (MMP-13), an essential enzyme responsible for the degradation of type II collagen in articular cartilage.[7,8]

Earlier research has shown that IL-8 concentrations are higher in the synovial fluid of individuals with OA than in healthy controls and are linked to enhanced MMPs activity and synovial inflammation. Experimental findings also indicate that blocking inflammatory pathways related to IL-8 may slow the progression of cartilage deterioration in OA models. Nevertheless, clinical data examining the relationship between systemic (serum) IL-8 concentrations and the severity of OA are still scarce and yield inconsistent results[7-9], indicating that the involvement of IL-8 in OA progression is multifaceted and may vary between the early and later stages of the disease.

The severity of OA is commonly assessed using the Kellgren–Lawrence (KL) radiographic classification, which evaluates structural joint changes based on osteophyte formation, joint space narrowing, and subchondral bone alterations. The KL grading system is widely used in epidemiological and clinical studies to classify OA severity from mild to severe.[10] Although radiographic classification provides valuable structural information, it does not capture early molecular and inflammatory changes, highlighting the need for exploratory studies investigating systemic inflammatory markers in relation to OA severity.

Considering this background, an exploratory cross-sectional study was undertaken to assess the relationship between serum IL-8 concentrations and the severity of knee OA. We hypothesized that serum IL-8 concentrations would be associated with the radiographic grading of knee OA. The findings from this study are intended to provide exploratory evidence to support further investigation into the systemic inflammatory processes involved in OA.

## Methods

The research employed a cross-sectional observational analytic design in patients with confirmed knee OA. The research was carried out in compliance with the Declaration of Helsinki and applicable national ethical standards. The Research Ethics Committee of Husada Utama Hospital granted ethical clearance for this study (No. 35/KEP-RSHU/X/2024; October

14, 2024). The study sites included Husada Utama Hospital in Surabaya and the Institute of Tropical Disease, Airlangga University. The study subjects consisted of seven elderly patients recruited from the Larasati Pondok OA Posyandu, Faculty of Medicine, Wijaya Kusuma University, using total sampling between November 2024 and January 2025. Given the small sample size, this study was designed as an exploratory analysis. All participants gave informed consent and fulfilled the predefined inclusion and exclusion criteria.

The inclusion criteria were patients diagnosed with knee OA based on clinical and radiographic criteria, aged ≥50 years, with body weight ≥40 kg, and experiencing pain in one or both knees. The exclusion criteria were patients with autoimmune diseases, hepatitis, renal disorders, bone malignancies, osteoporosis, or radiographic findings showing no evidence of OA.

The primary variable was serum IL-8 concentrations, measured as a systemic inflammatory marker using a Bio-Rad iMark™ Microplate Reader. Serum IL-8 concentrations were categorized into low, moderate, and high groups based on quartile distribution because no standardized clinical cut-off values for IL-8 in OA were available. The severity of OA was assessed using knee radiographs based on the Kellgren–Lawrence classification by specialist radiologists at the Radiology Department of Husada Utama Hospital. Statistical analysis was conducted using the Spearman correlation test in SPSS version 25, taking into account the limited sample size and the nonparametric distribution of the data.

**Result**

The study included seven older individuals diagnosed with knee OA. Each participant met the eligibility requirements and completed the research without any exclusions. The distribution of OA severity based on the KL classification is presented in Table 1. Among the seven participants, four (57.14%) had grade 2 OA and three (42.86%) had grade 3 OA.

**Table 1.** Distribution of osteoarthritis severity based on Kellgren–Lawrence classification (N=7)

| Osteoarthritis Severity | Frequency | Percentage |
|---|---|---|
| 2 | 4 | 57.14% |
| 3 | 3 | 42.86% |

The distribution of serum IL-8 concentrations among the study participants is presented in Table 2. Serum IL-8 concentrations were categorized into low, moderate, and high groups based on sample quartile distribution due to the absence of established clinical cut-off values.

**Table 2.** Distribution of serum IL-8 concentrations among study participants (N=7)

| Serum IL-8 concentrations (pg/mL) | Frequency | Percentage |
|---|---|---|
| Low (IL-8 < 113.85) | 2 | 28.57% |
| Moderate (113.85 ≤ IL-8 < 136.5) | 3 | 42.86% |
| High (IL-8 ≥ 136.5) | 2 | 28.57% |

Spearman's rank correlation analysis was conducted to evaluate the association between serum IL-8 concentrations and the severity of OA. The results demonstrated a strong negative correlation between serum IL-8 concentrations and OA severity ($r = -0.866$, $P = 0.012$), suggesting that serum IL-8 concentrations decreased as disease severity increased (Table 3). Given the small sample size, these findings should be regarded as exploratory and interpreted with caution.

**Table 3.** Association between serum IL-8 concentrations and osteoarthritis severity

| Serum IL-8 concentrations | OA Severity | | Total n (%) | Correlation Coefficient | *P*-value |
|---|---|---|---|---|---|
| | Grade 2, n (%) | Grade 3, n (%) | | | |
| Low | 0 (0%) | 2 (100%) | 2 (100%) | | |
| Moderate | 2 (66.67%) | 1 (33.33%) | 3 (100%) | -0.866 | 0.012 |
| High | 2 (100%) | 0 (0%) | 2 (100%) | | |
| **Total (Percentage)** | **4 (57.14%)** | **3 (42.86%)** | **7 (100%)** | | |

## Discussion

Results from this study indicated that higher severity of knee OA was significantly associated with lower serum IL-8 concentrations, indicating that IL-8 concentrations are relatively elevated in the early stages of the disease and tend to decline as OA becomes more severe. Despite the small sample size, these results suggest that serum IL-8 may serve as a potential early systemic biomarker representing inflammatory activity during the initial phase of OA.

Osteoarthritis is currently recognized as a low-grade chronic inflammatory disease involving complex interactions among chondrocytes, synoviocytes, immune cells, and inflammatory mediators such as cytokines and chemokines.[11] IL-8 is a proinflammatory chemokine produced by chondrocytes and synoviocytes and plays an important role in neutrophil recruitment and activation within joint tissues.[11,12] Neutrophil activation may

accelerate cartilage degradation through the release of proteolytic enzymes and inflammatory mediators, thereby contributing to OA progression.[11]

Increased IL-8 concentrations in both plasma and synovial fluid have been documented in individuals with knee OA, supporting its role in the disease's pathogenesis.[13] The findings of the present study indicate that IL-8 concentrations, which are higher during the early stage of OA, tend to decline as the disease advances. This observation aligns with earlier reports demonstrating that IL-8 is linked to clinical manifestations as well as biomarkers of bone and cartilage metabolism and has been proposed as a potential marker for early detection, evaluation of disease severity, and monitoring of progressive damage to cartilage and subchondral bone.[14,15]

However, the association between systemic IL-8 concentrations and OA severity remains inconsistent across studies. García-Manrique et al. reported that synovial fluid IL-8 was associated with clinical severity, whereas plasma IL-8 was not, indicating heterogeneity in systemic inflammatory biomarker findings.[7] Several studies have indicated that IL-8 concentrations in synovial fluid may serve as a more robust clinical marker of OA severity than serum IL-8, possibly due to complex biological processes or systemic compensatory mechanisms.[7,14] The observed reduction in serum IL-8 concentrations in advanced OA could represent negative feedback regulation of systemic inflammation or a shift from an active inflammatory stage toward a later phase dominated by structural degeneration.

Most previous studies have focused on synovial fluid biomarkers that reflect local joint inflammation; however, these procedures are invasive and less feasible for population-based screening.[13] Evidence regarding serum IL-8 as a systemic biomarker remains limited and heterogeneous. This study contributes exploratory evidence to this research gap by demonstrating a significant negative correlation between serum IL-8 concentrations and OA severity, highlighting the potential role of IL-8 as an early systemic inflammatory biomarker in OA.

This study has certain limitations, notably the small sample size and the cross-sectional design, which does not allow conclusions about causality. In addition, potential confounding factors such as obesity and metabolic conditions were not fully controlled and may influence systemic inflammatory biomarker concentrations.[7,11] Therefore, longitudinal studies with larger sample sizes and adequate control of confounding factors are required to validate these findings.

## Conclusion

This study indicates that serum IL-8 concentrations tend to be higher in the early stages

of knee OA and decrease as disease severity progresses, suggesting that systemic inflammatory activity may be more prominent in the initial phase of the disease. These results indicate that serum IL-8 could be regarded as a potential early marker of systemic inflammatory involvement in OA. However, the findings should be interpreted with caution because of the small sample size and the cross-sectional nature of the study. Additional longitudinal research involving larger populations is required to validate these observations and to further define the clinical significance of serum IL-8, including its possible utility in early diagnosis and in monitoring disease progression.

**Conflicts of Interest**

The authors state that there are no competing interests.

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